Inclusion/Exclusion Criteria for National Cancer Institute (NCI) Sponsored Clinical Trials

NCI Recommended Protocol Text and Guidance based on Joint Recommendations of the American Society of Clinical Oncology (ASCO) and Friends of Cancer Research (Friends)

The NCI's Cancer Therapy Evaluation Program (CTEP) in the Division of Cancer Treatment and Diagnosis (DCTD) brought together NCI Divisions, Offices and Centers that sponsor NCI clinical trials to review the published recommendations by ASCO and Friends in October 2017 (https://www.asco.org/research-progress/clinical-trials/clinical-trial-eligibility-criteria). ASCO, Friends, and the US Food and Drug Administration (FDA) examined specific eligibility criteria (i.e., brain metastases, minimum age, HIV infection, and organ dysfunction and prior and concurrent malignancies) to determine whether to recommend definitions to extend trials to a broader population. The below table includes the ASCO/Friends recommendations and the modifications by the NCI after further review and additional input from pharmacology experts on the NCI's Investigational Drug Steering Committee. NCI's Experimental Therapeutics Clinical Trials Network (ETCTN) and NCI's National Clinical Trials Network (NCTN) will utilize these broadened eligibility criteria in clinical trials going forward and active trials may be modified when feasible. CTEP has incorporated these criteria into the Generic Protocol Template updated September 4, 2018 posted on the CTEP website.

To implement these inclusion criteria in NCI-sponsored trials, add the text from the fourth column of the following tables (with the header "NCI Inclusion Criteria Template Language") to the eligibility section of your protocol with guidance from column two.

Please note: The Generic Protocol Template was updated on September 26, 2018 with an update on page 8 including:

Criteria updated	**September 4th version**	**September 26th version**
Liver function test AST(SGOT)/ALT(SGPT)	≤2.5 × institutional ULN	≤3 × institutional ULN

Additional guidance was also added:

- *These are guidelines that may or should be modified based on protocol-specific or drug development-specific needs.*

The updated template is posted on the CTEP website:

- https://ctep.cancer.gov/protocolDevelopment/templates_applications.htm

NCI Recommended Protocol Text and Guidance based on Joint ASCO/Friends Recommendations

Brain Metastases

Criterion	NCI Guidance	ASCO Inclusion Criteria Template Language	NCI Inclusion Criteria Template Language

Patients with treated/stable brain metastases	These recommendations do not apply to:
	• Trials designed specifically for primary brain cancers, e.g., GBM.
	• Trials designed specifically for brain metastases
	  ○ Radiation
	  ○ Systemic agent for a specific disease with the specified trial objective of evaluating brain metastases response to treatment (lung, melanoma, breast)
		Patients with treated brain metastases are eligible if there is no evidence of progression for at least 4 weeks after CNS-directed treatment, as ascertained by clinical examination and brain imaging (MRI or CT) during the screening period.	Patients with treated brain metastases are eligible if follow-up brain imaging after CNS-directed therapy shows no evidence of progression.
			
			(**Note:** in specific trials, it may be necessary to add a time factor regarding the follow-up brain imaging, but this should be as lenient as medically indicated.)

Criterion	NCI Guidance	ASCO Inclusion Criteria Template Language	NCI Inclusion Criteria Template Language
Patients with new or progressive brain metastases (active brain metastases) or leptomeningeal (LMD) disease ***– early-phase trials***	Consider inclusion of an LMD cohort in early phase trials of drugs with anticipated CNS activity when relevant in the specific disease type under study. Consideration of CSF pharmacokinetic measurements is encouraged in this context. <u>Guidance for inclusion in early-phase trials</u> Patients with active brain metastases should be included early in clinical development when there is strong scientific rationale for likelihood of benefit based on molecular pathways or histology as well as preclinical data. - For drugs/modalities with less robust preclinical information on potential CNS activity, inclusion of patients with active brain metastases should still be considered, particularly if brain metastases are common in the intended-use population. - The inclusion of a CNS-specific cohort can provide valuable dosing and preliminary efficacy data to either support or refute inclusion in later phase trials. The mechanism of action of the drug or predicted blood-brain barrier (BBB) penetration should not necessarily influence a decision to include such patients. In addition, preclinical studies of intact BBB penetration are not necessarily reflective of blood-tumor barrier penetration.	No template language provided for inclusion criteria. <u>Template for exclusion:</u> (If patients with LMD are to be excluded, the following wording is suggested to avoid unnecessary exclusion of patients with imaging-only equivocal findings.) No known LMD.	Patients with new or progressive brain metastases (active brain metastases) or leptomeningeal disease are eligible if the treating physician determines that immediate CNS specific treatment is not required and is unlikely to be required during the first cycle of therapy.

Criterion	NCI Guidance	ASCO Inclusion Criteria Template Language	NCI Inclusion Criteria Template Language
Patients with new or progressive brain metastases (active brain metastases) or leptomeningeal disease – ***later-phase trials***	When possible, inclusion of an LMD cohort in later-phase trials may be useful to provide access to investigational agents and to generate additional safety and efficacy data. <u>Guidance for inclusion in later-phase trials:</u> - Ideally, data from earlier-phase trials, in concert with the strength of the scientific rationale and preclinical data, can inform decisions on inclusion of patients with active brain metastases in later-phase trials. - When such data are not available, a few potential trial designs could allow patients with active brain metastases to enroll, either as a parallel cohort or as a defined subset within the larger clinical trial.	No template language provided for inclusion criteria. <u>Template for exclusion:</u> (If patients with LMD are to be excluded, the following wording is suggested to avoid unnecessary exclusion of patients with imaging-only equivocal findings.) No known LMD.	Patients with new or progressive brain metastases (active brain metastases) or leptomeningeal disease are eligible if the treating physician determines that immediate CNS specific treatment is not required and is unlikely to be required during the first cycle of therapy.

Patients Younger than Age 18 Years

Criterion	NCI Guidance	ASCO Inclusion Criteria Template Language	NCI Inclusion Criteria Template Language
Patients younger than age 18 years	Pediatric-specific cohorts should be included in early-phase trials when there is strong scientific rationale for likelihood of benefit, based on molecular pathways or histology as well as preclinical data. Investigators and their industry collaborators are encouraged to discuss the inclusion of pediatric patients in the drug development plan early in the development process; and determine when it is relevant to study the agent in pediatric cancers. For studies that plan to include patients age younger than age 18, a pediatric oncologist co-investigator must be involved with the study and be responsible for writing the pediatric version of the informed consent.	a) Adolescent/pediatric patients age *[protocol author to insert age minimum and maximum specific to the study under consideration]* will be included after enrollment of adult patients after safety and toxicity in the adult population have been established. Participating sites will be notified when adolescent/pediatric patient enrollment may begin. b) Adolescent/pediatric patients age *[protocol author to insert age minimum and maximum specific to the study under consideration]* will be included starting one dose cohort behind the current adult cohort in which there are no dose-limiting toxicities identified. Participating sites will be notified when enrollment onto the adolescent/pediatric stratum may begin. c) Adolescent/pediatric patients age *[protocol author to insert age minimum and maximum specific to the study under consideration]* will be included in age- specific cohorts that will be staggered starting one dose cohort behind the current adult cohort in which there are no dose- limiting toxicities identified. Participating sites will be notified when each adolescent/pediatric cohort enrollment may begin. d) Adolescent/pediatric patients age *[protocol author to insert age minimum and maximum specific to the study under consideration]* are included in this trial in a separate cohort that will accrue simultaneous to the adult cohort *[specify age 18 and older or protocol-specific upper age limit]*.	No template language needed as the lower age limit should be added to the eligibility criteria. ASCO/Friends template language offers potential options for certain studies.

Criterion	NCI Guidance	ASCO Inclusion Criteria Template Language	NCI Inclusion Criteria Template Language
Patients with HIV infection	HIV-related eligibility criteria should be straightforward and focus on: - Current and past CD4 and T-cell counts - History (if any) of AIDS-defining conditions - Status of HIV treatment Patients with HIV infection should be treated using the same standards as other patients with co-morbidities. Anti-retroviral therapy should be considered a concomitant medication.	HIV-infected patients who are healthy and have a low risk of AIDS-related outcomes are included in this trial.	HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.
For patients with evidence of chronic hepatitis B virus (HBV) infection and/or patients with a history of hepatitis C virus (HCV) infection	Patients with HBV and/or HCV should be treated using the same standards as other patients with co-morbidities. Therapy should be considered a concomitant medication.	None provided	For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated. Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.

Prior or Concurrent Malignancies

Criterion	NCI Guidance	ASCO Inclusion Criteria Template Language	NCI Inclusion Criteria Template Language
Prior or concurrent malignancies	Patients with prior or concurrent malignancies should be eligible, especially when the risk of the malignancy interfering with either safety or efficacy endpoints is very low.	Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen should be included.	Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.

Organ Function: Cardiac, Liver, and Kidney

Criterion	NCI Guidance	ASCO Inclusion Criteria Template Language	NCI Inclusion Criteria Template Language
Cardiac function	Investigator assessment of a potential participant's risk for heart failure should use a validated clinical classification system (e.g., the New York Heart Association Functional Classification). Patients with active cardiac disease may be eligible after assessment of cardiac function by a cardiologist.	None provided	Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class 2B or better.
Liver function	Liver function tests used to determine eligibility should be assessed relative to institutional normal ranges, not a universal cutoff point. These are guidelines that may be modified based on protocol-specific or drug development-specific needs.	None provided	Total Bilirubin: ≤ institutional upper limit of normal (ULN) AST(SGOT)/ALT(SGPT): ≤3 × institutional ULN
Kidney function	For agents for which renal excretion is not a major route of clearance and for which renal toxicity is not an issue, the threshold for creatinine clearance should be >30 mL/min.	Patients with creatinine clearance >30 mL/min (measured using Cockcroft-Gault equation or the estimated glomerular filtration rate from the Modification of Diet in Renal Disease Study) are included in the study. Established dose- modification strategies can allow safe and effective administration.	**ETCTN and Phase I trials** GFR ≥60 mL/min/1.73m2 unless data exists supporting safe use at lower kidney function values, no lower than 30 mL/min/1.73m2. OR **NCTN trials (mostly large phase II and III trials)** GFR ≥50 mL/min/1.73m2 unless data exists supporting safe use at lower kidney function values, no lower than 30 mL/min/1.73m2.

Formula to estimate renal function using serum creatinine

1. Estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (Ann Intern Med. 2009;150:604-612).

Formulae:

Race and Sex	Serum Creatinine, *µmol/L (mg/dL)*	Equation
Black		
Female	≤62 (≤0.7)	$GFR = 166 \times (Scr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 166 \times (Scr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 163 \times (Scr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 163 \times (Scr/0.9)^{-1.209} \times (0.993)^{Age}$
White or other		
Female	≤62 (≤0.7)	$GFR = 144 \times (Scr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 144 \times (Scr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 141 \times (Scr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 141 \times (Scr/0.9)^{-1.209} \times (0.993)^{Age}$

Scr in mg/dL; Output is in mL/min/1.73m^2 and needs no further conversions.

2. Estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) Study (Ann Intern Med. 2006;145:247-254).

175 x $SCr^{-1.154}$ x $age^{-0.203}$ x 0.742 (if female) x 1.212 (if black)

Output is in mL/min/1.73m^2 and needs no further conversions.

3. Estimated creatinine clearance (Clcr) by the Cockcroft-Gault (C-G) equation (Nephron 1976;16:31-41).

$$CLcr\ (mL/min) = \frac{[140 - age\ (years)] \times weight\ (kg)}{72 \times serum\ creatinine\ (mg\ /\ dL)} \{\times 0.85\ for\ female\ patients\}$$

Followed by conversion to a value normalized to 1.73m^2 with the patient's BSA.